REMARKS

Applicants hereby request reconsideration of the present application in view of the foregoing amendments and the following remarks. The amendments to the claims are in accord with the suggestions of the Examiner. Claims 1, 15 and 20 have been re-written to incorporate a structure from claim 14 and to eliminate overlap between R_5 and R_7. The attachment of the heterocyclic group, specified in those claims is supported, *inter alia*, in the specification at page 11. Most of the amendments merely delete Markush members that the Examiner found objectionable. No new matter is presented. Upon entry of the foregoing amendments, claims 1-7 and 9-27 will be pending.

REJECTIONS UNDER 35 USC § 112, SECOND PARAGRAPH

The Office asserts twenty-one bases of rejection under this section of the statute. While Applicants respectfully traverse, they have addressed points 3 - 9, 11 - 15, 17, 20 and 21 by deleting recitations found objectionable or by adding clarifying language. These amendments were made solely to focus the issues in this case, and thus expedite prosecution. Applicants do not by these or any other amendments acquiesce to the rejections, and they reserve the right to pursue the deleted subject matter in the future.

In response to points 1 and 2, the cited species from claim 14 is incorporated into claims 1, 15 and 20 and R_7 has been eliminated. In response to point 10, referring to the meaning of "carbohydrate moiety," attention is directed to the specification at pages 4 and 5-9, where ample exemplary support is given. It is submitted, accordingly, that this term is sufficiently definite to comport with the statutory requirements.

In point 16, the Office questions the nature of the substituents when Q is a substituted alkyl. Attention is directed to the specification at page 7, lines 22-27, where clear exemplary support is provided. It is submitted that this term also meets the requirements of the law. Re-written claim 14 responds to point 18. Point 19 is addressed with reference to claim 1, which recites that Q may be a "substituted or unsubstituted . . . $C_{(2\text{-}10)}$ alkenyl," which provides antecedent basis for the term at issue.

REJECTIONS UNDER 35 USC § 112, FIRST PARAGRAPH

The rejection under 35 USC 112, first paragraph is a reiteration of the same rejection that was maintained in the parent. See Action of October 18, 1996.[1] It is founded in the "how to use" prong of the statute. Applicants respectfully traverse.

Applicants first make the following points: (1) claims 1-7, 9-14 and 20-27 are ***compound*** claims and, therefore, embody ***non-therapeutic*** utilities as well as therapeutic ones; (2) enablement must be evaluated taking into account the claim scope (MPEP §§ 2164.01 and 2164.08); and (3) imputing therapeutic limitations for the purpose of evaluating enablement, or any other purpose, is improper.

The first basis of rejection is that "the dosage problem remains." The Office contends, in essence, that the dosage information provided in the specification is confusing. Applicants submit, first, that specific dosage information is unnecessary to enable the instant invention and, second, that an allegedly unclear statement in the specification does not affect enablement.

As stated before, clinical data are not required for enablement. See MPEP § 2107.02. Here, the specification contains both *in vitro* and animal data relevant to dosage; the next step is human clinical trials. Thus, the Office improperly holds the instant invention to an enablement standard that can only be met with clinical data. This is true *a fortiori* for claims 1-7, 9-14 and 20-27, which are directed to ***compounds*** and, thus, do not rely on pharmaceutical applications for enablement. Hence, insofar as the rejection of claims 1-7, 9-14 and 20-27 relies on imputed therapeutic limitations, it is improper.

Furthermore, in view of the instant specification, the clinical data needed to determine suitable dosage requires only the kind and amount of routine experimentation endemic to any clinical trial. Indeed, determining a suitable, non-toxic dosage regimen is a primary purpose of clinical trials. Using standard dose escalation protocols, this determination is routinely made for ***every drug*** undergoing clinical investigation. Accordingly, considering the vast number of

[1] All quotations below refer to this Action, since it is the last in which this rejection was fully articulated.

drugs that have undergone clinical investigation, there is a ***very high level of skill*** in the pharmaceutical and chemical arts.

The PTO will also note that the instant compounds are substituted xanthine derivatives and that the clinician would have experience with substituted xanthines. See, for example, GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 7th ed., pp. 589-603 (Macmillan Publishing Co., N.Y. 1985). Further, at least some embodied compounds are structurally similar to lisofylline, a drug that has been the subject of clinical investigation. Hence, considering the clinical experience with structurally similar compounds and the high level of skill in the art, it is reasonable to conclude that determining suitable dosage would not require undue experimentation.

Second, this conclusion is unaltered with respect to alleged confusion in the specification. The specification offers general guidance to the clinical investigator, who will recognize that the specification does not teach radical departures from established protocols and common sense. Accordingly, any alleged confusion in the specification would be overlooked, or at least viewed in light of conventional clinical wisdom. The artisan would not, therefore, be unable to practice the instant invention based on the belief that the drug must be administered "1000 times a day." The level of skill in this art is sufficiently high that any such perception would immediately be dismissed.

Furthermore, the specification provides ample enabling guidance with respect to dosage. For example, the first full paragraph on page 9 discloses a suitable daily dose of "about 0.1 mg/kg to about 1000 mg/kg." The next paragraph discloses doses of "about 50 mg to about 5000 mg per day." Finally, Examples 22-24 provide guidance with respect to *in vitro* systems and Example 25 provides the treatment of dogs with representative compounds and provides further dosage guidance. In view of this guidance and the high level of skill in this well-developed art, one could use the invention with only the usual, routine experimentation inherent in the art. Accordingly, Applicants submit that this ground of rejection fails to establish a *prima facie* case and, therefore, request its withdrawal.

The PTO also asserts the existence of allegedly non-operative embodiments as evidence of non-enablement. It is contended "[t]he notion that these compounds are all prodrugs is simply not credible [because] [o]rdinary ethers cannot be significantly hydrolyzed by the body ...." Applicants submit that the Examiner is improperly reading a "prodrug" limitation into the claims.

The PTO is reminded that claims 1-7, 9-14 and 20-27 are directed to ***compounds*** which, due to selective chemical structures, provide for selective control of the extent and rate of hydrolysis of these compounds to a hydroxyl-substituted xanthine compound. A need for such differing hydrolytic potential may arise in the context of a synthetic method, not exclusively in the context of a therapeutic application. The Examiner is also reminded that, although directed to "pharmaceutical composition[s]," claims 15-19 do not contain a "prodrug" limitation either. Even if the claims were directed to "prodrugs," the existence of non-operative embodiments is insufficient to conclude that the invention is not enabled. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984).

The PTO finally claims that "applicants have not presented evidence that lisofylline has actually been shown useful for anything." Thus, the Examiner's reasoning appears to be as follows: (a) the instant compounds are prodrugs of lisofylline; (b) the sole usefulness of the inventive compounds is as lisofylline prodrugs; (c) lisofylline is not "useful for anything;" therefore (d) the present compounds are not "useful for anything." Applicants reiterate that the instant claims are not directed to "prodrugs" of lisofylline or "prodrugs" of any other drug, rather they are directed to **compounds**. The specification amply describes utilities for them. Applicants still submit that this rejection a disguised (improper) rejection for lack of utility, instead of one for lack of enablement.

CONCLUSIONS

In view of the foregoing, Applicants submit that the present claims are in condition for allowance. Should the Examiner have any questions regarding the present application or believe that further discussion will advance prosecution, the Examiner is invited to contact the undersigned at the number listed below.

Respectfully submitted,

26 October 1998
Date

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